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Randomized Phase I/II Trial of a Macrophage-Specific Immunomodulator (PGG-Glucan) in High-Risk Surgical Patients

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Objective
The safety and efficacy of PGG-glucan in surgical patients at high risk for postoperative infection who underwent major thoracic or abdominal surgery were determined.

Summary Background Data
Recent studies have reported a 25% to 27% infectious complication rate in patients undergoing major surgery with an average cost per infected patient of $12,000. The efficacy of PGG-glucan pretreatment in prevention of sepsis has been demonstrated in rodent models for gram-negative and gram-positive bacterial and yeast infections. *In vitro* studies have demonstrated enhanced microbial killing by monocytes and neutrophils in healthy volunteers after PGG-glucan administration. Thus, PGG-glucan may play a role in decreasing the infectious complication rate in patients undergoing major surgery.

Methods
A double-blind, placebo-controlled randomized study was performed in 34 high-risk patients undergoing major abdominal or thoracic surgery.

Results
There were no adverse drug experiences associated with PGG-glucan infusion. Patients who received PGG-glucan had significantly fewer infectious complications (3.4 infections per infected patient *vs.* 1.4 infections per infected patient, $p = 0.05$), decreased intravenous antibiotic requirement (10.3 days *vs.* 0.4 days, $p = 0.04$) and shorter intensive care unit length of stay (3.3 days *vs.* 0.1 days, $p = 0.03$).

Conclusions
PGG-glucan is safe and appears to be effective in the further reduction of the morbidity and cost of major surgery.

Table 1. IMPACT OF INFECTION ON HOSPITAL COSTS

Major Gastrointestinal Surgery	National Survey Data*	Arch Surgery†	Patients/Year‡
Hospital days			
Uninfected patients	12	17	397,000
Infected patients	22	28	144,000
Infection rate	27%	25%	
Cost/infected patient	$12,980	$12,542	

* Martin T. Miller Associates, 1993 U.S. hospital discharge data.
† Shulkin, et al, Arch. Surg. 1993; 128: 449-452.
‡ CDC national data, 1990.

Despite improvements in both preoperative and postoperative care, major gastrointestinal (GI) surgery still is accompanied by a substantial postoperative infectious complication rate. A recent independent survey found a 27% infection rate in patients undergoing major GI surgery in the United States.[1] A separate study reported by Shulkin et al., found similar results with a 25% infection rate among patients undergoing major GI surgery.[2] In both reports, infected patients had a significantly longer hospital length of stay and associated increased costs. (Table 1)

PGG-glucan (Betafectin, Alpha-Beta Technology, Inc., Worcester, MA) is a glucose polymer that stimulates and enhances specific humoral and cellular responses to challenge by infectious organisms. PGG-glucan (poly-(1-6)-B-D-glucopyranosyl-(1-3)-B-D-glucopyranose) belongs to a class of compounds known generically as B-glucans and is a highly purified, soluble, active molecule derived from a proprietary, nonrecombinant yeast strain of *Saccharomyces cerevisiae*.[3] (Fig. 1) Unlike other B-glucan preparations, PGG-glucan lacks *in vivo* pyrogenic and inflammatory effects resulting from cytokine induction, but retains potent immunostimulatory properties.

Initial *in vitro* characterizations of PGG-glucan have demonstrated that it has a high affinity for B-glucan receptors of human monocytes and neutrophils and binds competitively to the receptor in a dose-dependent manner at concentrations significantly below those required for other natural B-glucan preparations derived from bakers' yeast.[4] Studies have shown that PGG-glucan significantly increases human neutrophils and macrophages *in vitro* microbicidal activity against *Staphylococcus aureus* without directly stimulating synthesis of the cytokines, interleukin-1 or tumor necrosis factor.[5,6] Numerous *in vivo* studies in mice and rats have shown that PGG-glucan administration improves survival rates compared with control animals after challenge with fungal (*Candida albicans*), gram-positive (*S. aureus*), and gram-negative (*Escherichia coli*) organisms.[7,8,9] Finally, PGG-glucan is free from the pyrogenic and inflammatory effects common to many biologic response modifiers and is nonantigenic.[10,11]

To date, two clinical trials of PGG-glucan have been completed in healthy volunteers. Results from these studies indicate that a single intravenous dose of PGG-glucan at 0.05 to 2.25 mg/kg was safe and well tolerated. Clinical assessments of physical conditions, vital signs, and electrocardiograms showed no clinically significant abnormalities. PGG-glucan treatment did not produce persistent fever, nausea, myalgia, or bone pain, which are common side effects noted after cytokine treatment. White blood cell counts showed transient increases in the total number of white cells, as well as increases in monocyte and neutrophil populations. These hematologic changes are consistent with results from preclinical studies of PGG-glucan and could indicate a clinically useful

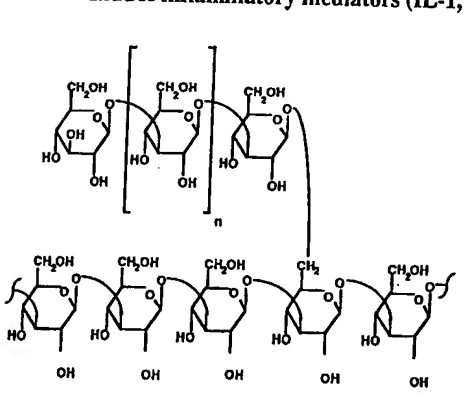

Figure 1. Structure of PGG-glucan.

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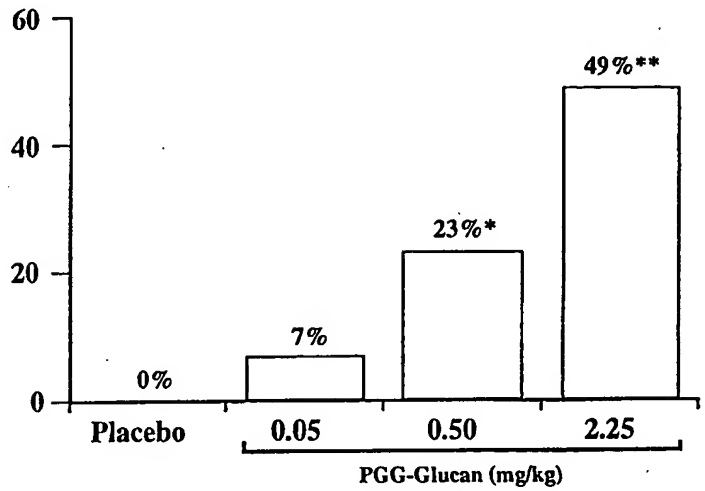

Figure 2. Effect of PGG-glucan on neutrophil and monocyte microbial killing activity in healthy volunteers. Result: dose-dependent increase in microbial killing activity (*$p < 0.10$, **$p < 0.05$). Reprinted with permission.

response to the drug. Leukocytes in blood samples from the 0.5 mg/kg and 2.25 mg/kg dose group showed an increase in microbial killing activity against *S. aureus*, with killing activity increasing from 7% at a dose of 0.05 mg/kg to 49% with a dose of 2.25 mg/kg.[12,13] (Fig. 2) Finally, pharmacokinetic analysis of PGG-glucan elimination demonstrated a two-compartment elimination model, with a $t_{1/2}$-alpha of 0.5 to 1 hour and a $t_{1/2}$-beta of 7 to 12 hours.[14]

PGG-glucan has been shown to improve immune function in a variety of animal models and more recently, in healthy volunteers. The absence of inflammatory or febrile consequences on administration led us to examine the role of PGG-glucan as immunoprophylaxis in surgical patients at high risk for postoperative infections. Therefore, the purpose of the study was to evaluate the safety and efficacy of PGG-glucan in surgical patients undergoing major thoracic or abdominal surgery.

MATERIALS AND METHODS

The study was performed at a single institution, the Deaconess Hospital, (Boston, MA) a tertiary referral center specializing in hepatobiliary, thoracic, vascular, oncologic surgery, and diabetes mellitus. Inclusion criteria included age > 18 years, scheduled major noncardiac thoracic or abdominal surgery—with the patient expected to be hospitalized for at least 5 days after surgery, ability to understand the requirements of the study, white blood cell count ≥ 4000/mm^3 and platelet count ≥ 100,000/mm^3. Patients were excluded from the study if they met any of the following criteria: renal failure requiring hemodialysis or peritoneal dialysis, Class III or Class IV New York Heart Association function cardiac status, active systemic infection at the time of enrollment, long-term preoperative total parenteral nutrition, scheduled chemotherapy or radiotherapy within 4 weeks before surgery or 2 weeks after surgery, known human immunodeficiency virus-positive serology, and pregnancy. A total of 34 patients were enrolled in the study, and 30 were evaluated. All four patients who were excluded had randomized to the PGG-glucan treatment group. Of these four patients, three had their surgery canceled, and one patient voluntarily withdrew from the study before undergoing surgery. Signed informed consent, which had been approved by the Institutional Review Board of the Deaconess Hospital, was obtained from each patient before enrollment in the study.

This was a randomized, double-blind, placebo-controlled Phase I/II study conducted from August 1992 through March, 1993. Patients were randomized in a 2:1 ratio to receive 0.5 mg/kg of PGG-glucan or saline placebo. Patients received multiple, sequential doses by intravenous infusion of 0.5 mg/kg of PGG-glucan or saline placebo 12 to 24 hours before surgery, 1 to 4 hours before surgery, 48 hours after surgery, and 96 hours after surgery. (Fig. 3) Patients were evaluated before surgery and until their discharge from the hospital. In addition, long-term follow-up was performed 4 and 8 weeks postoperatively.

PGG-glucan was provided by Alpha-Beta Technology, Inc., in sterile 30-mL vials, each containing 20 mL of PGG-glucan at a concentration of 1 mg/mL in sodium chloride injection USP. Physiologic saline placebo was provided by the pharmacy of the Deaconess Hospital. Three vials of PGG-glucan were provided for each patient randomized to active treatment. Sodium chloride injection USP was used to make up the remaining infusion volume of 50 to 200 mL. Dosing occurred as a continuous intravenous infusion (by pump) for 1 hour.

Two types of sponsor blood samples were collected during the study: sponsor sample I and II. Sponsor sam-

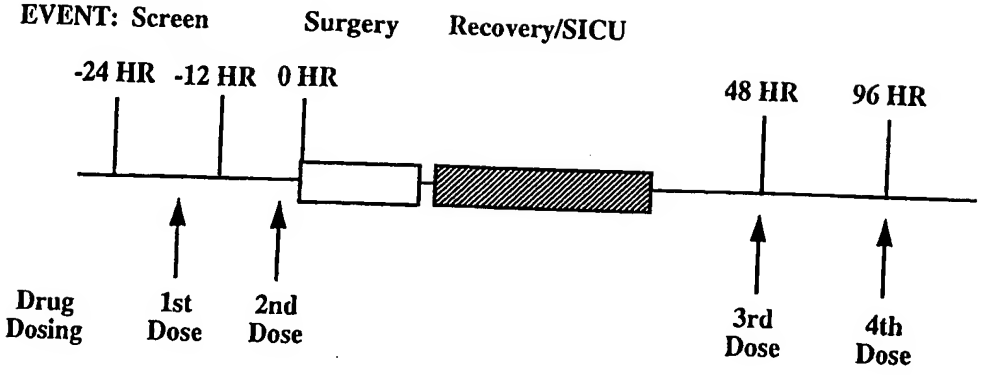

Figure 3. Randomized double-blind, placebo-controlled study in 30 patients undergoing major thoracic or abdominal surgery. Exclusion criteria: active preoperative infection long-term total parenteral nutrition, preoperative chemotherapy, human immunodeficiency virus positive, dialysis-dependent renal failure. Patients were randomized to receive PGG-glucan or saline at a 2:1 ratio. PGG-glucan was administered by intravenous infusion of 0.5 mg/kg.

ple I was drawn at baseline day 1, postoperative day 1 and postoperative day 5. Two 4-mL aliquots of citrated blood were collected and stored at room temperature for delivery within 4 hours to Alpha-Beta Technology, Inc., for assessment of leukocyte microbicidal activity. Neutrophils and macrophages were purified by Ficoll-Hypaque density gradient centrifugation and analyzed for microbicidal activity against *S. aureus, E. coli,* and *C. albicans,* with and without stimulation by phorbol ester. Results of sponsor sample assays for microbicidal activity were considered as surrogate markers of PGG-glucan activity. These assays were blinded to the treatment status of the patients from whom the blood samples were collected. Sponsor sample II was drawn at baseline, postoperative day 10, discharge, and at week 4 and week 8 long-term follow-up visits. Seven milliliters of blood were drawn to obtain 2 mL of serum, which subsequently was stored at −20 C for evaluation of antibodies to PGG-glucan.

Each patient was monitored for PGG-glucan tolerance. All clinically significant adverse experiences observed or reported during the clinical trial that were considered serious or noteworthy were recorded. Laboratory values that were significantly out of a normal range were considered adverse experiences.

Statistical analyses were done using the chi square test and analysis of variance. Differences were considered to be significant when the p value was < 0.05.

RESULTS

Table 2 lists the surgical procedures that the patients underwent, including a comparison of the risk factors for infection between the two groups. There were 13 patients in the control group and 17 patients in the PGG-glucan group. The incidence of "clean-contaminated" wound classification (as compared with a "clean" classification) was slightly higher in the PGG-glucan group *versus* control subjects (56% *vs.* 46%). The mean duration of surgery was similar between the two groups (4.1 hrs *vs.* 4.2 hrs.) The PGG-glucan group was slightly older (70 yrs *vs.* 61 yrs) and had more patients with American Society of Anesthesiologists scores ≥ 3 (62% *vs.* 42%). There were significantly more diabetics requiring insulin in the PGG-glucan group (36% *vs.* 0%, $p < 0.05$). There were no statistical differences in the percentage of GI surgeries (65% *vs.* 46%) or the amount of major blood loss between the two groups (18% *vs.* 31%). All patients in both treatment groups received standard preoperative antibiotics according to the preference of their surgeon, and there was no difference in the overall type or number of prophylactic antibiotics given.

All adverse drug experiences (ADE) were reported in compliance with the FDA regulations. There was no significant difference in the total ADEs between the two groups with 137 (44%) ADEs in the control group and 178 (56%) ADEs in the PGG-glucan group. (Table 3) There were no PGG-glucan-related ADEs; the majority of ADEs were clinically insignificant, and most were considered typical abnormalities that occur during the postoperative course. There was one death in the PGG-glucan group, which was secondary to liver failure in a patient with stage IV ovarian carcinoma.

Mean white blood cell counts were comparable for both treatment groups at all four timepoints analyzed; screening (control 7.5 ± 2.4 *vs.* PGG-glucan 6.9 ± 1.7), postoperative day 2 (control 12.0 ± 4.3 *vs.* PGG-glucan 11.1 ± 2.7), postoperative day 4 (control 9.1 ± 4.0 *vs.* PGG-glucan 8.7 ± 2.7) and postoperative day 10 (control 8.3 ± 3.6 *vs.* PGG-glucan 8.9 ± 2.6).

Table 4 summarizes the efficacy endpoints of the study. There was a statistically significant reduction in the number of infectious complications in those patients who received PGG-glucan compared with controls. There were 17 infectious complications in five control patients compared with 7 infectious complications in five PGG-glucan patients ($p = 0.02$). Examined another way, there was a significant reduction in the number of infections per infected patient (3.4 infections per infected patient in control group *vs.* 1.4 infections per infected patient in the PGG-glucan group, $p = 0.05$) Table 5 further characterizes the type and number of con-

Table 2. PROCEDURES PERFORMED AND ANALYSIS OF RISK FACTORS FOR INFECTION

PGG-Glucan
- Bilateral oophorectomy and transhepatic stent placement
- AAA resection
- Hemicolectomy and cholecystectomy
- Hepatic Lobectomy
- Aortobifemoral bypass
- Hemicolectomy and ventral herniorrhaphy
- Aortobifemoral bypass
- Pancreaticoduodenectomy
- Extended hemicolectomy, small bowel resection
- Cystectomy
- Abdominoperineal resection
- AAA resection with ureteral stents
- Extensive lysis adhesions, liver biopsy
- Total abdominal colectomy
- Sigmoid colectomy
- Cryoablation of hepatic metastases
- Pancreaticoduodenectomy

Control
- Gastrectomy
- AAA resection
- AAA resection, transverse colostomy
- AAA resection, ventral herniorrhaphy
- Excision mediastinal mass
- Sigmoid colectomy with repair colovesical fistula
- Distal pancreatectomy, nephrectomy, adrenalectomy.
- Excision abdominal sarcoma
- Resection perineal tumor, cystectomy
- Hemicolectomy
- Hemicolectomy
- Aortobifemoral bypass
- Sigmoid colectomy

Risk Factor	Control (n = 13)	PGG-Glucan (n = 17)	p Value
Clean-contaminated	46%	56%	NS
Surgery duration (mean)	4.1 hr	4.2 hr	NS
ASA ≥ 3	46%	62%	NS
Age (mean)	61 yr	70 yr	NS
Diabetes (insulin requiring)	0	36%	<0.01
GI surgery	46%	65%	NS
Blood loss > 1800 mL	31%	18%	NS
Prophylactic antibiotics	100%	100%	NS

firmed (culture-positive) infections that occurred during the study. In all categories of infections (blood culture positive, pneumonia, urinary tract infection, wound, and other), there was a reduction in the number of confirmed infections among those patients who received PGG-glucan. When patients had more than one site (e.g., wound and urine) with a positive culture or developed another pathogen at a particular site after an adequate antimicrobial regimen, these were counted as separate positive cultures.

As a separate measure of infectious complications, an Eastern Cooperative Oncology Group scoring system was used to determine the severity of clinical symptomatology (i.e., morbidity) of these infections. A grade 0 represents no clinical symptomatology; whereas grades 1 through 3 represent increasingly severe symptomatology (fever, white blood cell count, etc.) associated with infection (Table 4). There was a significant reduction in the severity of symptomatology in those patients who received PGG-glucan, with 11 of 17 patients having grades 1 through 3 compared with 10 of 13 control patients ($p = 0.05$).

Another marker of infectious complications is the number of anti-infective medications that patients required postoperatively. Table 6 depicts the use of anti-infective (both antibiotic and antifungal) medications between the two groups. There was no difference in the type or number of prophylactic antibiotics that the two groups received. However, beginning on postoperative day 3 and continuing until discharge, there was a significant reduction in the total number of anti-infective medications ($p = 0.005$) and the number of medications per patient ($p = 0.04$) in the PGG-glucan group.

Table 3. SUMMARY OF ADVERSE DRUG EXPERIENCES

	Control (n = 13)	PGG-Glucan (n = 21)
Total adverse drug experiences (ADEs) (%)	137 (44%)	178 (56%)
Mean ADEs per patient	10.5	8.4*

* NS *vs.* control.
No PGG-glucan-related ADEs; one death not drug related.

Table 4. SUMMARY OF EFFICACY ENDPOINTS

Endpoint	Control (n = 13)	PGG-Glucan (n = 17)	p Value
Confirmed infections (no. of patients)	17 (5)	7 (5)	0.02
Intravenous antibiotic use*			
Total days of treatment	134	6	0.005
Mean days per patient	10.3	0.4	0.04
Infection severity (Grade 0/Grade 1–3)†	3/10	11/6	0.05
Intensive care unit days	3.3	0.1	0.03

* Excludes prophylactic antibiotics.
† ECOG scores: Grade 0—no infection; Grade 1—minor infection, no fever; Grade 2—minor infection with fever; Grade 3—severe infection with positive culture; Grade 4—systemic sepsis.

Table 5. NUMBER OF CONFIRMED (CULTURE-POSITIVE) INFECTIONS

Infection Type (no. of patients)	Control (n = 13)	PGG-Glucan (n = 17)
Blood culture positive	5 (3)	1 (1)
Pneumonia	2 (2)	0
Urinary tract infection	4 (4)	1 (1)
Wound	6 (3)	3 (3)
Other	0	2 (2)
Total	17 (5)	7* (5)

* $p < 0.02$.

Table 7. DURATION OF HOSPITALIZATION AND INTENSIVE CARE UNIT DAYS

Group	Hospital Days	Intensive Care Unit Days
Control	17.0 ± 15.5	3.3 ± 6.3
PGG-glucan	12.3 ± 6.1	0.1 ± 0.4*

* $p < 0.03$.

The hospital length of stay was shorter (12.3 ± 6.1 days *vs.* 17.0 ± 15.5 days) for patients who received PGG-Glucan than for control subjects, although this did not reach statistical significance. There was however, a significant reduction ($p = 0.03$) in intensive care unit (ICU) length of stay (0.1 ± 0.4 days *vs.* 3.3 ± 6.3 days) among those patients who received PGG-glucan compared with control subjects (Table 7). In addition, comparison of infected *versus* uninfected patients revealed that the increased hospital and ICU length of stay was most likely secondary to the infectious complications because there was no significant difference among uninfected patients (Table 8).

The net absolute mean difference in percent killing post-treatment *versus* pretreatment is reported in Table 9. This calculation subtracts the baseline percent killing from each postsurgical sample and shows that, as a result of surgery, both basal and phorbol ester-induced microbicidal activity were reduced. PGG-glucan treatment generally stimulated the phorbol ester-induced microbicidal activity of monocytes against *S. aureus* on days 1 and 5 and against *C. albicans* on day 5. PGG-glucan stimulated the phorbol ester-induced microbicidal activity of polymorphonuclear leukocytes against *E. coli* on day 1 and against *C. albicans* on days 1 and 5. None of the *in vitro* tests of microbicidal activity were statistically significant.

DISCUSSION

Infectious complications continue to represent a major morbidity for patients undergoing high-risk thoracic or abdominal surgery. The cost of these infectious complications is considerable and is estimated to add an additional $12,000 to the cost of hospitalization per infected patient. Despite broad improvements in perioperative management, ICU technology, and antibiotic therapy, there has been no recent evidence to suggest that postoperative infectious complications are diminishing in number or severity.[15,16] This suggests that a new approach to these problems that could enhance postoperative immune function (i.e., immunoprophylaxis) is required. This study sought to examine the safety and efficacy of a novel compound (PGG-glucan) as a means of upregulating polymorphonuclear leukocyte and monocyte function, thus reducing the number and severity of infectious complications in a group of high-risk patients undergoing major thoracic or abdominal surgery.

Biologically derived glucan, either in crude form or partially purified, has long been known to improve immune function in a variety of animal models[17] and more recently, after trauma in man.[18,19] This has been attrib-

Table 6. USE OF ANTI-INFECTIVE MEDICATIONS

Group	Study Period				
	Day-1 Preoperative	Day 0–2	Day 3–7	Day 7 to Discharge	Day 0 to Discharge
Control (n = 13)	35 (2.7)	8 (0.6)	9 (0.7)	27 (2.1)	44 (3.4)
PGG-glucan (n = 17)	40* (2.4)	9* (0.5)	1† (0.1)	8‡ (0.5)	19‡ (1.1)

Number of medications (medications per patient).
* NS.
† $p < 1+ > 0.02$.
‡ $p < 1+ > 0.005$.

Table 8. DURATION OF HOSPITALIZATION AND INTENSIVE CARE UNIT DAYS IN INFECTED *VS.* UNINFECTED PATIENTS

	Hospital Days	Intensive Care Unit Days
Uninfected patients		
Control (n = 8)	9.1 ± 2.0	0.2 ± 0.7
PGG-glucan (n = 12)	10.0 ± 2.6	0.2 ± 0.4
Infected patients		
Control (n = 5)	30.4 ± 19.0	8.2 ± 8.0
PGG-glucan (n = 5)	19.4 ± 7.3	0.2 ± 0.4*

* $p < 0.05$ vs. control.

uted to the release of interleukin-1 by stimulation of the glucan receptor on monocytes and macrophages.[20] PGG-glucan, a highly purified compound derived from an engineered strain of yeast, has been shown to remain immunologically effective, but does not elicit or prime interleukin-1 or tumor necrosis factor production.[21] The absence of inflammatory or febrile consequent to administration (presumably because of this lack of cytokine response) led us to investigate its role as immunoprophylaxis in surgical patients at high risk for postoperative infections. Preclinical data from animal studies indicated that PGG-glucan could stimulate leukocytosis and phagocytic activity, resulting in a protection against infection.

This study was a single-center Phase I/II, randomized, double-blind, placebo-controlled trial that examined the safety and efficacy of PGG-glucan infusion in 34 male and female patients undergoing major abdominal or thoracic surgery who were deemed at high risk for infectious complications. This study represents the first assessment of PGG-glucan in a patient population. Despite the fact that there were a number of factors that biased against the potential efficacy of PGG-glucan (e.g., increased number of diabetics, higher percentage of clean-contaminated [as compared with clean] cases, and an older average age) patients who received PGG-glucan had a significant decrease in the number and severity of postoperative infectious complications. In addition, the severity of these infections, as determined by the Eastern Cooperative Oncology Group scoring system, was less in the PGG-glucan treated patients. It also was found that patients who received PGG-glucan had a significant reduction in the the number of anti-infective medicines prescribed and days in the ICU. Finally, there were no serious adverse experiences associated with PGG-glucan administration.

Based on the presumed mechanism of action, PGG-glucan would be expected to be effective against systemic infections or infections removed from the site of local contamination by surgery. Although the number of infected patients did not differ between the two groups (5 of 13 placebo-control patients *vs.* 5 of 17 PGG-glucan patients) the number of infectious complications per infected patient was reduced significantly in the patients treated with PGG-glucan (3.4 infections per infected patient in the control group *vs.* 1.4 infections per infected patient in the PGG-glucan group, $p = 0.05$). This would suggest two possible explanations for the demonstrated efficacy of PGG-glucan. In some instances, the initial infection may not be preventable by PGG-glucan administration, but the subsequent response of the host to that infection may be altered favorably to limit wider dissemination or greater severity. In this action, PGG-glucan may be exerting an ameliorating impact on the usually immunosuppressive consequences of infectious complications, manifested (perhaps) as an increase in the phagocytic properties of polymorphonuclear leukocytes and monocytes. A second broad possibility, which is not exclusive of the former, is that immunoprophylaxis with PGG-glucan raises the general host resistance to infection, thereby limiting the initial number of infection sites and their subsequent severity. Future work will be directed at refining the assay to help elucidate the exact mechanism of the action of PGG-glucan.

The occurrence and clinical relevance of postoperative infections was assessed in several ways, including the use of anti-infective (antibiotic and antifungal) medications and the morbidity of the infection. There was a significant reduction in the number of anti-infective medica-

Table 9. NET DIFFERENCE IN PERCENT KILLING BY PHAGOCYTIC CELLS FROM BETAFECTIN-TREATED *VS.* CONTROL PATIENTS

	Basal Microbicidal Activity		PMA-Induced Microbicidal Activity	
Test System	Day 1	Day 5	Day 1	Day 5
Macrophages				
Staphylococcus aureus	−9	42	8	11
Escherichia coli	10	−24	−4	−15
Candida albicans	19	32	−2	6
Polymorphonuclear cells				
S. aureus	−56	−38	−4	−1
E. coli	9	−45	17	−6
C. albicans	−1	25	22	35

Calculation was average mean % killing by Betafectin-treated phagocytic cells minus average mean % killing control patient phagocytic cells.
PMA = phorbol myristate acetate.

tions that the patients treated with PGG-glucan required. Because the clinicians were blinded in the study, these results support the contention that the infectious complications in the control group were sufficiently serious to warrant systemic treatment. Finally, an Eastern Cooperative Oncology Group scoring system was employed as an additional measure of the clinical severity of the symptomatology that accompanied these infectious complications. Although the Eastern Cooperative Oncology Group scoring system was not specifically designed for surgical infectious complications, it is a useful measure of clinical severity. Once again, there was a significant decrease in the severity of the symptomatology among those patients who were treated with PGG-glucan. Taken together, these three separate markers of efficacy (number of confirmed infections, use of anti-infective medications and severity of symptomatology) suggest that PGG-glucan may play a role in decreasing the infectious complications of major surgery.

The increased cost associated with infectious complications is due, in large part, to the increased hospital and ICU length of stay that accompanies these infections and the diagnostic evaluation and anti-infective treatment rendered during that increased length of stay.[22,23] Patients treated with PGG-glucan had a decreased hospital length of stay ($p = 0.2$) and a significant decrease in ICU length of stay. The decrease in ICU length of stay could be attributed to a decrease in the number and severity of infectious complications, because there was no difference in ICU length of stay among those patients that did not become infected (Table 9). Because the average cost per infected patient has been estimated at $12,000, the net savings possible with this therapy will be determined by the ultimate cost of PGG-glucan and its administration, which currently is not known.[24]

The results of *in vitro* assays performed in this study indicated that monocytes from patients treated with PGG-glucan showed a trend toward increased microbicidal killing activity against *S. aureus* and *C. albicans*, although this did not reach statistical significance. Because improved phagocytosis or killing function by monocytes, macrophages, or polymorphonuclear leukocytes remains the most likely mechanism for the improved outcome vis-a-vis the number and severity of infections, it may require the development of more sensitive *in vitro* tests with less innate variability in the clinical setting to clearly identify this change in function.

This is the first report of a randomized trial of a novel compound (PGG-glucan); it examines its safety and efficacy in reducing postoperative infectious complications in patients at high risk for postoperative infection. Although the study size was limited (30 patients), all efficacy parameters (number and severity of infectious complications, use of anti-infective medications, and ICU length of stay) suggested a potential benefit to PGG-glucan administration. This preliminary trial demonstrated a favorable safety and efficacy profile for this new compound that justifies broader investigation into its ultimate utility for these purposes.

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